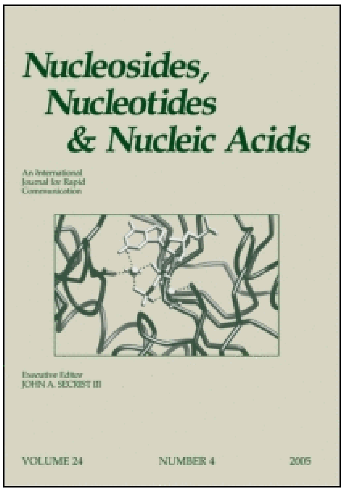

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Gun Ha Baik[a]; Bong Young Chung[a]; Chang-Hyun Oh[b]; Jung-Hyuck Cho[b]; Ok Hyun Ko[c]; Joon Hee Hong[c]
[a] Department of Chemistry, Korea University, Anam-dong, Sungbuk-ku, Seoul, South Korea [b] Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul, South Korea [c] College of Pharmacy, Chosun University, Kwangju, South Korea

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Novel Synthesis of 4′*C*-Aryl-Branched Acyclic Nucleoside Using [3,3]-Sigmatropic Rearrangement

Gun Ha Baik,[1] Bong Young Chung,[1] Chang-Hyun Oh,[2] Jung-Hyuck Cho,[2] Ok Hyun Ko,[3] and Joon Hee Hong[3,*]

[1]Department of Chemistry, Korea University, Anam-dong,
Sungbuk-ku, Seoul, South Korea
[2]Medicinal Chemistry Research Center, Korea Institute of Science
and Technology, Seoul, South Korea
[3]College of Pharmacy, Chosun University,
Kwangju, South Korea

ABSTRACT

A very efficient synthetic route for preparing a novel 4′-*C*-aryl branched-1′,2′-seco-2′,3′-dideoxy-2′,3′-didehydro-nucleoside is described. Mesylate **7** was successfully synthesized via a Horner-Wadsworth-Emmons reaction and a [3,3]-sigmatropic rearrangement, with which an adenine base was coupled by nucleophilic substitution conditions (K_2CO_3, 18-*Crown*-6, DMF) to give the target nucleoside **9**.

Key Words: Acyclic nucleoside; [3,3]-Sigmatropic rearrangement; Antiviral agent.

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*Correspondence: Joon Hee Hong, College of Pharmacy, Chosun University, Kwangju 501-759, South Korea; Fax: 82-62-222-5414; E-mail: hongjh@mail.chosun.ac.kr.

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INTRODUCTION

The discovery of novel nucleosides for use as antiviral and anticancer agents has been the ambition of nucleoside chemists for decades. Since the emergence of the HIV pandemic, extensive effort have been concentrated on various modifications of the sugar moiety of nucleosides, which have resulted in FDA approved anti-HIV agents such as AZT,[1] ddC,[2] ddI,[3] d4T,[4] 3TC,[5] and Abacavir.[6] In addition, several nucleosides used as anti-HBV agents including L-F-ddC,[7] and L-FMAU[8] have been synthesized. The recent approval of Bis(POC) PMPA[9] by the FDA as an anti-HIV agent has strongly warranted a further search of novel nucleosides in this class.

More recently, several branched-nucleosides[10] have been synthesized and evaluated as potent antitumor or antiviral agents. Among them, 4′α-*C*-ethenyl[11] and 4′α-*C*-ethynyl[12] nucleosides, which possess an additional double or triple bond at the 4′-position were reported to have potent antiviral and antitumor activities. Encouraged by these interesting structures and antiviral activities, this study aimed to synthesize novel classes of nucleosides, which are hybrids of branched carbocyclic and 1′,2′-seco-acyclic nucleoside analogues showing marginal anti-HIV activity (Fig. 1).

RESULTS AND DISCUSSION

As depicted in Sch. 1, the synthetic route is straightforward. It was envisaged that a [3,3]-sigmatropic rearrangement[13] of **4** would produce the desired quaternary carbon **5** with the suitable functional groups. Subjecting **7** to nucleophilic substitution conditions and desilyation produced the desired nucleoside **9**.

The silyl protection of the alcohol of a commercially available starting material, 2-hydroxy acetophenone **1**, followed by a Horner-Wadsworth-Emmons (HWE) reaction,[14] provided the α,β-unsaturated ethyl ester **3** in a cis/trans isomeric mixture. It is not necessary to separate the isomers, as they will be merged into one isomer in subsequent reaction. Ester **3** was reduced to the allylic alcohol **4** by using diisobutylaluminum hydride (DIBALH) in an 83% yield. The compound **4** was subjected to a normal Johnson's orthoester A Claisen rearrangement using

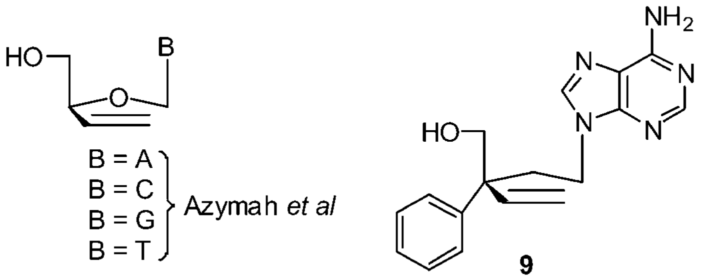
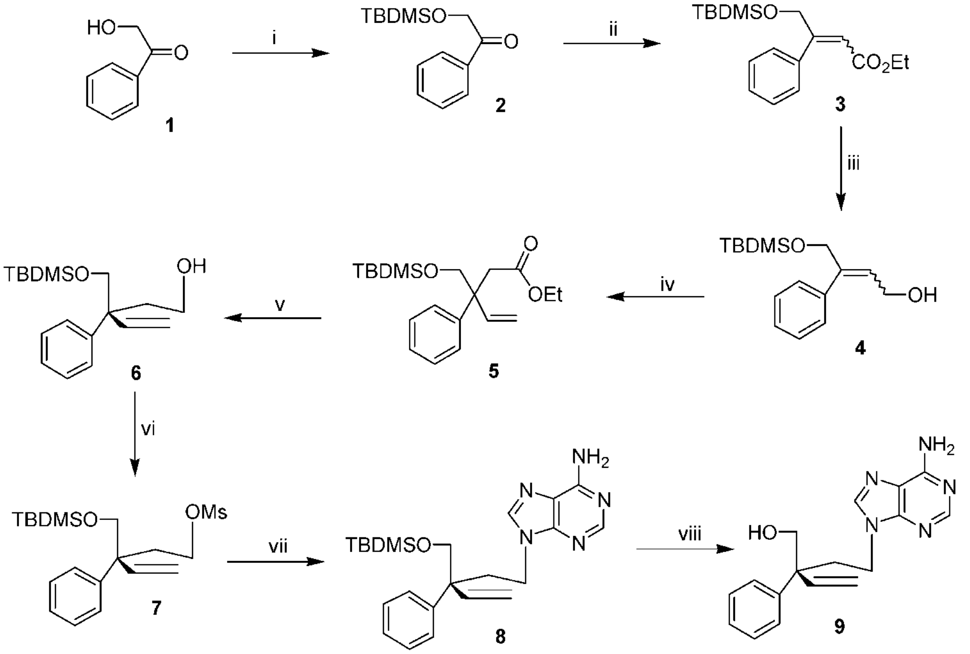


Figure 1.



Scheme 1. Reagents: i) TBDMSCl, Imidazole, CH_2Cl_2, rt, 5 h, 90%; ii) Triethylphosphonoacetate, NaH, THF, 0°C, 1 h, 83%; iii) DIBALH, CH_2Cl_2, −20°C, 3 h, 83%; iv) Triethyl orthoacetate, propionic acid, ovemight, 130–135°C, 81% v) DIBALH, CH_2Cl_2, −20°C, 2 h, 89%; vi) MsCl, CH_2Cl_2, TEA, 0°C, 1 h, 83%; vii) adenine, K_2CO_3, 18-C-6, DMF, 90°C, overnignt, 50%; viii) TBAF, THF, rt, 4 h, 86%.

triethyl orthoacetate gave the γ,δ–unsaturated ester **5** in an 81% yield. The slow addition of DIBALH to a solution of ester **5** in CH_2Cl_2 at −20°C furnished alcohol **6** in an 89% yield. The hydroxyl group of **6** was mesylated with methanesulfonyl chloride (MsCl) in an anhydrous CH_2Cl_2 solvent to give the key intermediate **7** in an 83% yield. The mesylate **7** was coupled with the nucleobase (adenine) under well-known nucleophilic substitution conditions (K_2CO_3, 18-*C*-6, DMF)[15] to give the adenine derivative **8** in a 50% yield. The deblocking of **8** was accomplished using tetrabutyl ammonium fluoride (TBAF) to furnish the final nucleoside **9** in an 86% yield. Although other analogs (Fig. 1) were previously reported by another group,[16] compound **9** is novel nucleoside based on an extensive literature search.

An antiviral assay of the synthesized nucleoside **9** against the human immunodeficiency virus 1 (HIV-1), the herpes simplex virus 1,2 (HSV-1, 2) and HCMV was performed. However, no significant antiviral activity or cytotoxicity up to 100 μM was found.

CONCLUSION

A novel acyclic nucleoside was successfully synthesized from the starting material, 2-hydroxy acetophenone. The strategy for elaborating the quaternary carbon is highly efficient and convenient. Furthermore, it has the flexibility for further applications to the synthesis of other novel acyclic and carbocyclic nucleosides.

EXPERIMENTAL SECTION

The melting points were determined on a Mel-tem II laboratory device and were uncorrected. The NMR spectra were recorded on a Bruker 300 Fourier transform spectrometer. The elemental analyses were performed at the Korea Basic Science Institute. The UV spectra were obtained on a Beckman DU-7 spectrophotometer. The TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out under N_2 unless otherwise specified. Dry dichloromethane, benzene and pyridine were obtained by a distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

2-(t-Butyldimethylsilyloxy)-acetophenone (2). To a solution of 2-hydroxy acetophenone **1** (10 g, 73.4 mmol) and imidazole (7.49 g, 110.1 mmol) in CH_2Cl_2 (150 mL), TBDMSCl (12.1 g, 80.74 mmol) was added slowly at 0°C, and stirred for 5 h at room temperature. The reaction solvent was evaporated under reduced pressure, and the residue was extracted with EtOAc (100 × 2). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (EtOAc/hexane, 1:7) to give compound **2** (16.5 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, $J = 7.2$ Hz, 2H), 7.46–7.30 (m, 3H), 4.79 (s, 2H), 0.80 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 197.42, 134.85, 133.22, 128.56, 127.83, 67.40, 25.78, 18.44, −5.36; Anal calc for $C_{14}H_{22}O_2Si$: C, 67.15; H, 8.86. Found: C, 66.97; H, 8.65.

(E) and (Z)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-enoic acid ethyl ester (3). To a suspension of sodium hydride (60% in mineral oil, 0.74 g, 18.5 mmol) in distilled THF triethyl phosphonoacetate (2.81 mL, 18.5 mmol) was added drop wise at 0°C and the mixture was stirred at room temperature for 1 h. Ketone **2** (4.63 g, 18.5 mmol) was added to this mixture and the mixture was stirred for 1 h. The solution was neutralized with AcOH, and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **3** (4.92 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.04 (m, 5H), 6.09, 5.93 (dt, $J = 1.3$, 1.8 Hz, 1H), 5.08, 4.23 (dd, $J = 0.9$, 2.1 Hz, 2H), 4.22, 3.90 (dq, $J = 6.9$, 6.9 Hz, 2H), 1.20, 0.95 (dt, $J = 6.9$, 6.9 Hz, 3H), 0.84, 0.65 (s, s, 9H), 0.02, −0.10 (s, s, 6H); Anal calc for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.66; H, 8.95.

(E) and (Z)-4-(t-Butyldimethylsilyloxy)-3-phenyl-but-2-en-1-ol (4). To a solution of **3** (5 g, 15.6 mmol) in CH_2Cl_2 (100 mL), DIBALH (34.3 mL, 1.0 M solution in hexane) was added slowly at −20°C, and stirred for 3 h at the same temperature. To the mixture, methanol (30 mL) was added. The mixture was stirred at room temperature for 3 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give the allylic alcohol **4** (3.6 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.07 (m, 5H), 5.99, 5.91 (dt, $J = 6.6, 6.6$ Hz, 1H), 4.31 (d, $J = 6.6$ Hz, 1H), 4.27 (s, 1H), 0.85, 0.81 (s, s, 9H), 0.02 (m, 6H); Anal calc for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.18; H, 9.26.

(±)-3-(t-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enoic acid ethyl ester (5). A solution of the allylic alcohol **4** (12 g, 43.09 mmol) in triethyl orthoacetate (200 mL) and 0.5 mL of propionic acid was heated at 130–135°C overnight. An excess of triethyl orthoacetate was distilled off and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give **5** (12.16 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.25 (m, 5H), 6.26 (dd, $J = 18.0, 11.1$ Hz, 1H), 5.31 (dd, $J = 11.4, 1.2$ Hz, 1H), 5.16 (dd, $J = 17.7, 0.6$ Hz, 1H), 4.10–3.99 (m, 4H), 3.00 (s, 2H), 1.18 (t, $J = 6.9$ Hz, 3H), 0.99 (s, 9H), 0.02 (d, $J = 8.1$, 6H); ^{13}C NMR ($CDCl_3$) δ 171.51, 143.17, 142.33, 127.82, 127.34, 126.30, 114.34, 67.73, 59.94, 48.70, 39.74, 25.76, 18.19, 14.07, −5.71; Anal calc for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25. Found: C, 68.69; H, 9.05.

(±)-3-(t-Butyldimethylsilyloxymethyl)-3-phenyl-pent-4-en-1-ol (6). To a solution of **5** (3.2 g, 9.18 mmol) in CH_2Cl_2 (50 mL), DIBALH (20.1 mL, 1.0 M solution in hexane) was added slowly at −78°C, and stirred for 2 h at the same temperature. To the mixture, methanol (10 mL) was added. The mixture was stirred at room temperature for 2 h, and the resulting solid was filtered through a Celite pad. The filtrate was concentrated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give **6** (2.5 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.28 (m, 5H), 5.82 (dd, $J = 17.4, 10.8$ Hz, 1H), 5.33 (d, $J = 10.7$ Hz, 1H), 5.13 (d, $J = 10.5$ Hz, 1H), 4.24 (t, $J = 6.9$ Hz, 2H), 3.80 (s, 2H), 1.72 (m, 2H), 0.90 (s, 9H), −0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 142.48, 141.65, 128.20, 127.32, 126.60, 115.09, 68.80, 67.72, 48.59, 34.18, 25.74, 18.13, −5.71; Anal calc for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87. Found: C, 70.26; H, 9.66.

(±)-1-*O*-Methanesulfonic acid-3-(t-butyldimethylsilyloxymethyl)-3-phenyl-pent-4-enyl ester (7). To a solution of alcohol **6** (2.5 g, 8.15 mmol) in anhydrous CH_2Cl_2 (30 mL), anhydrous triethyl amine (2.27 mL, 16.3 mmol) and MsCl (1.39 g, 12.2 mmol) was added at 0°C. The mixture was stirred at the same temperature for 1 h, and quenched by adding a cold saturated $NaHCO_3$ solution (2 mL). The mixture was extracted with CH_2Cl_2 (100 mL) and water (50 mL). The organic layer was dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to give **7** (2.6 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.29 (m, 5H), 6.02 (dd, $J = 17.4, 10.8$ Hz, 1H), 5.34 (d, $J = 9.9$ Hz, Hz, 1H), 5.17 (d, $J = 17.7$ Hz, 1H), 4.25 (t, $J = 6.9$ Hz, 2H), 3.83 (s, 2H), 2.93 (s, 3H, mesyl), 2.44 (m, 2H), 0.95 (s, 9H), −0.02 (s, 6H); Anal calc for $C_{19}H_{32}O_4SSi$: C, 59.33; H, 8.39. Found: C, 59.68; H, 8.54.

(±)-9-[3-(t-Butyldimethylsilyloxymethyl)-3-phenyl-4-pent-1-enyl] adenine (8). A solution of mesylate **7** (560 mg, 1.45 mmol), K_2CO_3 (401 mg, 2.9 mmol), 18-crown-6 (329 mg, 1.26 mmol), adenine (195 mg, 1.45 mmol) in dry DMF (10 mL) was stirred overnight at 90°C. The mixture was cooled to room temperature and concentrated under vacuum. The residue was diluted with brine (10 mL) and extracted with CH_2Cl_2 (10 mL × 4). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:15) to give **8** (307 mg, 50%) as a white solid: mp 167–170°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.31 (s, 1H), 7.68 (s, 1H), 7.42–7.26 (m, 5H), 6.67 (br s, 2H), 6.13 (dd, $J = 17.7$, 11.1 Hz, 1H) 5.39 (dd, $J = 10.8$, 0.6 Hz, 1H), 5.27 (d, $J = 18.0$ Hz, 1H), 4.19 (t, $J = 8.1$ Hz, 2H), 3.90 (dd, $J = 14.1$, 9.9 Hz, 2H), 2.57–2.48 (m, 2H), 0.87 (s, 9H), −0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.44, 152.20, 149.75, 142.51, 141.64, 140.09, 128.25, 127.42, 126.67, 115.42, 68.70, 49.02, 40.73, 25.76, 18.15, −5.70; Anal calc for $C_{23}H_{33}N_5OSi$: C, 65.21; H, 7.85; N, 16.53. Found: C, 65.44; H, 7.69; N, 16.32.

(±)-9-[3-(t-Hydroxymethyl)-3-phenyl-4-pent-1-enyl] adenine (9). To a solution of **8** (250 mg, 0.59 mmol) in tetrahydrofuran (10 mL), tetrabutylammonium fluoride (TBAF) (0.88 mL, 1.0 M solution in THF) was added at 0°C. The mixture was stirred at room temperature for 4 h, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1:7) to give **9** (160 mg, 86%) as a white solid: mp 182–185°C; UV (H_2O) λ_{max} 261.0 nm; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.12 (s, 1H, H-8), 8.08 (s, 1H), 7.41–7.15 (m, 5H), 6.05 (dd, $J = 15.9$, 11.1 Hz, 1H), 5.27 (d, $J = 11.7$, 1H), 5.17 (s, 1H), 4.87 (t. $J = 6.4$ Hz, Hz, 1H, D_2O exchangeable), 4.01 (br s, 2H), 3.76 (m, 2H), 2.36 (br d, $J = 7.8$ Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 155.91, 152.30, 149.39, 143.25, 142.46, 140.60, 128.07, 127.35, 126.10, 114.62, 66.68, 48.58, 34.67, 23.05, 13.47; Anal calc for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64. Found: C, 66.38; H, 6.31; N, 22.48.

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